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Kinetic and safety assessment for salicylic acid nitration by nitric acid/acetic acid system

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Abstract

The nitration process of salicylic acid for the production of the important intermediate 5-nitrosalicylic acid is studied from thermokinetic and safety points of view. Investigations carried out by considering, as process deviations, the loss of the thermal control point out the possibility of runaway phenomena due to the occurrence of polynitration reactions. Isothermal experiments are carried out in various conditions to assess the involved reaction network and reaction kinetics.

Keywords: Nitration; Salicylic acid; Thermal explosion; Adiabatic calorimetry; Modelling

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1. Introduction

5-Nitrosalicyic acid is an important intermediate for chemical and pharmaceutical industries. The corresponding 5-amine (mesalazine) is currently used as active species for the treatment of various pathologies such as ulcerative colitis and Crohn's disease [1,2]. Its production through nitration processes, using the classic mixed acid, results into yields lower than 50% and in some difficulties with the separation of the reaction mixture. Even in recent years patents appeared claiming the possibility of producing this species from salicylic acid with interesting yields [3,4]. However, a literature survey indicated that there is still a need to find new nitrating systems to overcome the difficulties associated with current production processes of 5-nitrosalicylic acid. An alternative system with respect to the classic "mixed acid" could be represented by the mixture nitric acid/acetic acid/acetic anhydride which has been found in the past to give good results with the nitration of phenol and the esterification of carnitine [5,6]. Nevertheless, one has to consider that this system is not free of explosion hazards arising from the formation of intermediate acetylnitrate. This species has been reported to undergo thermal decomposition even during the storage at ambient temperature [7,8]. Moreover, recently some authors investigated the tendency of the system nitric acid/acetic anhydride/acetic acid to decompose, from kinetic and thermal point of view [9], thus concluding that it can give rise to runaway phenomena which are sustained by the violent decomposition of intermediate acetylnitrate.

On the basis of these indications it could be argued that if the formation of acetylnitrate would be inhibited or reduced, a more inherently safe system could be found. A first attempt to move in this direction could be done by using the system nitric acid/acetic acid, in which a reduced formation – if any – of acetylnitrate could be expected. Previous investigations confirmed the possibility of using the system HNO_3/CH_3COOH for the nitration of salicylic acid with yields to 5-nitrosalicylic acid significantly higher than those found with a classic mixed acid.

Therefore, the present work aims at studying the kinetics and the safety aspects of the nitration process of salicylic acid by means of the system nitric acid/acetic acid.

2. Experimental

The investigations have been carried out under adiabatic and isothermal conditions. For adiabatic experiments ARC (Columbia Scientific Industries, USA) and Phi-Tec (Hazard Evaluation Laboratory, UK) calorimeters have been used.

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Nomenclature

C_i	concentration of *i*th species ($\mathrm{mol\,l^{-1}}$)
C_org	concentration of generic organic ($\mathrm{mol\,l^{-1}}$)
C_p	mean specific heat of reacting mixture ($\mathrm{J\,K^{-1}\,g^{-1}}$)
E_i	activation energy of reaction for *i*th species ($\mathrm{kJ\,mol^{-1}}$)
ΔH_i	heat of reaction for *i*th species ($\mathrm{kJ\,mol^{-1}}$)
k_i^0	pre-exponential factor of reaction for *i*th species (rate expression depending)
ms	sample mass (mixture) (g)
n, *m*	reaction orders (dimensionless)
φ	thermal inertia (dimensionless)
r_i	rate of reaction for *i*th species ($\mathrm{mol\,(l\,min)^{-1}}$)
R	universal constant of gas ($\mathrm{J\,mol^{-1}\,K^{-1}}$)
t	time (min)
T	temperature (K)
T_0	initial temperature (K)
ΔT_ad	adiabatic temperature rise (K)
V	sample volume (mixture) (l)
z	stoichiometric coefficient (dimensionless)

In all the runs performed in the ARC calorimeter, in the usual heat/wait/search mode [10] with a slope sensitivity of $0.02\,\mathrm{K\,min^{-1}}$, samples of about 2 g of reacting mixtures ($\mathrm{Cps} = 2.1\,\mathrm{J\,g^{-1}\,K^{-1}}$) and Stainless Steel ARC bomb ($\mathrm{Cpb} = 0.4186\,\mathrm{J\,g^{-1}\,K^{-1}}$) were used. Phi-Tec calorimeter has been used in standard “closed can”. In these runs, the glass reactor (magnetically stirred, $V = 0.048\,\mathrm{l}$) was primarily charged with the substrate and assembled into the calorimeter, afterwards, by using a vacuum pump, it was partially purged (initial absolute pressure 0.2 bar) and the system allowed to stabilize at the initial temperature. Once the desired initial conditions were attained, a suitable pre-heated solution (to the same temperature as the reactor) of nitric acid/acetic acid was fed in batch mode into the reactor (a typical values of the total mass of the reacting mixture was of about 34 g). The last operation being achieved by suction using the standard connections of the device.

For isothermal experiments, a RADEX oven [11] equipped with a closed high pressure stainless steel reactor ($V = 0.004\,\mathrm{l}$) and driven by a PC Combilab (SystAG, CH) has been used. Since the reactors do not allow any external addition during the course of the reaction, chemical mixtures were prepared at ambient temperature outside the oven by dissolving a suitable amount of reagents (nitro-derivatives of the salycilic acid) in the proper solution HNO_3/acetic acid. Once the reactor was charged, it was transferred in the oven previously heated to the desired initial temperature and allowing the mixure to react for the desired reaction time.

Whenever necessary, after a preliminary thermal quenching at ambient temperature, samples collected in both types of experiments have been submitted to HPLC analysis by using a Hewlett-Packard model 1100 II equipped with an UV–vis detector and a Phenomenex Synergi 4 μ polar RP/80 ° column. The following operating conditions have been adopted: column temperature, 298.16 K; mobile phase composition (vol/vol-%), 80% buffer solution [CH_3OH (5%), H_3PO_4 (0.4%), H_2O (94.6%)] and 20% acetonitrile; flow rate, $1\,\mathrm{ml\,min^{-1}}$; the signals have been acquired at 240, 280, 350 nm.

3. Results and discussion

It is well known that, among possible chemical process deviations, the loss of the thermal control is one of the most frequent and dangerous one [12]. In fact, in this case, an initial positive drift of the reactor temperature may result first into a runaway event and in some cases into a thermal explosion with severe damages to people and plants.

Preliminary experiments of nitration of salicylic acid with the proposed system at ambient or near ambient temperature indicated that main products are 5-nitrosalicylic and 3-nitrosalicylic acid, with a minor occurrence of 2-nitrophenol. Since it is well known that an increase of the temperature favours polynitration reactions of aromatics with the formation of di- and trinitroderivatives [13], it can be expected that a complex reaction network can arise from the successive nitrations of three above-reported species. A set of experiments has been thus planned and performed to identify the reactions occurring when the temperature increases. The nitration of 5-nitrosalicylic and 3-nitrosalicylic acid has been separately investigated at respectively 353.16 and 333.16 K using the RADEX oven (initial system composition for 5-nitrosalicylic acid: 0.0194 g of substrate, 0.0267 g of HNO_3, 0.002 l of acetic acid; for 3-nitrosalicylic acid: 0.018 g of substrate, 0.0248 g of HNO_3, 0.002 l of acetic acid). Collected results are shown in the Figs. 1 and 2. Some gathered information point out that both the compounds are partially converted into 3,5-dinitrosalicylic acid (3,5-DNS), whereas 2,4-dinitrophenol (2,4-DNP) and 2,6-dinitrophenol (2,6-DNP) result, respectively, from 5-nitrosalicylic (5-NS) and 3-nitrosalicylic acid (3-NS).

In both the experiments, a minor occurrence of picric acid (PA) was observed. Similar experiments on 2-nitrophenol (2-NP) (initial system composition: 0.0013 g of 2-NP, 0.0267 g of HNO_3, 0.002 l of acetic acid) at 313.16 K showed the formation

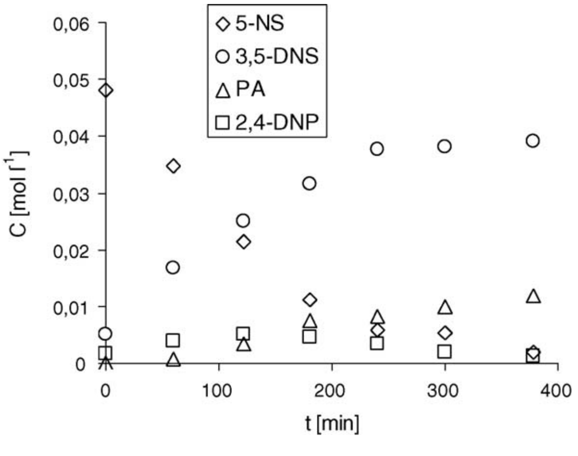

Fig. 1. Nitration of 5-nitrosalicylic acid at 353.16 K.